PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 11245/485762	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/41372	International filing date *(day/month/year)* 24 December 2002 (24.12.2002)	Priority date *(day/month/year)* 26 June 2002 (26.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12P 12/08, 21/08; A61K 39/395 and US Cl.: 530/387.3; 435/326; 424/133.1		
Applicant IMCLONE SYSTEMS INCORPORATED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 January 2004 (26 .01.2004)	21 April 2005 (21.04.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized Officer Phuong Huynh Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/41372

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1–34 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 35-42, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-49, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/41372

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 6-23, 42 and 43	YES
	Claims 1-5 and 24-41	NO
Inventive Step (IS)	Claims 6-23, 42 and 43	YES
	Claims 1-5 and 24-41	NO
Industrial Applicability (IA)	Claims 1-43	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 6-23 and 42-43 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed invention.

Claims 1-5, and 24-41 lack novelty under PCT Article 33(2) as being anticipated by Lu et al (Cancer Research October 2001, Vol 61 pages 7002-7008).
Lu et al teach an antibody such as bifunctional diabody having a first binding site specific for a first VEGF receptor such as KDR and a second VEGF receptor such as Flt-1 (see entire document, Figure 1, in particular). The reference antibody binds specifically to the extracellular domain of the KDR and Flt receptors and thereby blocking the binding of VEGF to its receptors (see abstract, in particular). Lu et al further teach a method of making the reference bifunctional diabody (see Materials and Methods, page 7003, in particular) and a method of neutralizing the activation of first and second VEGF receptors using the reference antibody in cell (see antimitogenic assay and Leukemia migration assay on page 7004-5, in particular). The reference bifunctional antibody is more efficient in inhibiting VEGF stimulated angiogenesis than the parent antibodies, suggesting this antibody is more potent and has greater implication in treatment of tumor growth (see abstract, page 7007, col. 2, in particular).

Claims 1-5, and 24-41 lack novelty under PCT Article 33(2) as being anticipated by Lu et al (J. Immunol. Methods November 1999, Vol 230 No. 1-2, pages 159-71)..
Lu et al teach an antibody such as bifunctional diabody having a first binding site specific for a first VEGF receptor such as KDR and a second VEGF receptor such as Flk-1 (see entire document, page 163, col. 2, in particular). The reference antibody binds specifically to the extracellular domain of the KDR and Flt receptors and thereby blocking the binding of VEGF to its receptors (see page 164, col. 2 Dual specificity of antibody, in particular). Lu et al further teach a method of making the reference bifunctional diabody (see Materials and Methods, page 164, construction and expression of diabody, in particular) and a method of neutralizing the activation of first and second VEGF receptors using the reference antibody in cell (see page 167, col. 2, in particular). The reference bifunctional antibody is a better choice of inhibiting VEGF induced activation of VEGF receptor and mitogenesis of human endothelial cells given the high avidity and effective crosslinking, suggesting its useful in treating cancer (see abstract, page 168-169, in particular).

Claims 1-5, and 24-41 lack an inventive step under PCT Article 33(3) as being obvious over Lu et al (Cancer Research October 2001, Vol 61 pages 7002-7008).
Lu et al teach an antibody such as bifunctional diabody having a first binding site specific for a first VEGF receptor such as KDR and a second VEGF receptor such as Flt-1 (see entire document, Figure 1, in particular). The reference antibody binds specifically to the extracellular domain of the KDR and Flt receptors and thereby blocking the binding of VEGF to its receptors (see abstract, in particular). Lu et al further teach a method of making the reference bifunctional diabody (see Materials and Methods, page 7003, in particular) and a method of neutralizing the activation of first and second VEGF receptors using the reference antibody in cell (see antimitogenic assay and Leukemia migration assay on page 7004-5, in particular). The reference bifunctional antibody is more efficient in inhibiting VEGF stimulated angiogenesis than the parent antibodies, suggesting this antibody is more potent and has greater implication in treatment of tumor growth (see abstract, page 7007, col. 2, in particular).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

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Lu et al teach an antibody such as bifunctional diabody having a first binding site specific for a first VEGF receptor such as KDR and a second VEGF receptor such as Flk-1 (see entire document, page 163, col. 2, in particular). The reference antibody binds specifically to the extracellular domain of the KDR and Flt receptors and thereby blocking the binding of VEGF to its receptors (see page 164, col. 2 Dual specificity of antibody, in particular). Lu et al further teach a method of making the reference bifunctional diabody (see Materials and Methods, page 164, construction and expression of diabody, in particular) and a method of neutralizing the activation of first and second VEGF receptors using the reference antibody in cell (see page 167, col. 2, in particular). The reference bifunctional antibody is a better choice of inhibiting VEGF induced activation of VEGF receptor and mitogenesis of human endothelial cells given the high avidity and effective crosslinking, suggesting its useful in treating cancer (see abstract, page 168-169, in particular).

Claims 1-43 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------